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10/568,235	02/14/2006	Terrance L. Geiger	SJ-03-0016A	9594

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EXAMINER	
HOWARD, ZACHARY C	
ART UNIT	PAPER NUMBER
1646	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/568,235	GEIGER, TERRANCE L.	
	Examiner	Art Unit	
	ZACHARY C. HOWARD	1646	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *26 March 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-19* is/are pending in the application.

4a) Of the above claim(s) *5,11,13 and 14* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-4,6-10,12 and 15-19* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☒ Claim(s) *1-19* are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *14 February 2006* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *2/14/06; 11/30/06*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Advisory Information

This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2). Therefore, Applicant must comply with the requirements of the sequence rules (37 CFR 1.821 - 1.825).

Figure 1 (filed on 2/14/06) contains two amino acid sequences, "SRRNRLLESD" and "SRRNRGGESD" that are not present in the Sequence Listing filed on 2/14/06.

37 CFR 1.821(c) requires that each sequence disclosed in the application appear separately in the "Sequence Listing," with each sequence further being assigned a sequence identification number, referred to as "SEQ ID NO." In order to comply with this rule, Applicant must provide a substitute computer readable form (CRF) copy of a "Sequence Listing" which includes all of the sequences recited in the claims and specification of the instant application that are encompassed by these rules, including the two sequences shown in Figure 1, a substitute paper copy of that "Sequence Listing", an amendment directing the entry of that paper copy into the specification, and a statement that the content of the paper and computer readable copies are the same and, where applicable, include no new matter, as required by 37 C.F.R. §§ 1.821(e) or 1.821(f) or 1.821(g) or 1.825(b) or 1.825(d).

Furthermore, the instant specification will also need to be amended so that it complies with 37 C.F.R. § 1.821(d) which requires a reference to a particular sequence identifier (SEQ ID NO:) be made in the specification and claims wherever a reference is made to that sequence. M.P.E.P. 2422.02 states: "It should be noted, though, that when a sequence is presented in a drawing, regardless of the format or the manner of presentation of that sequence in the drawing, the sequence must still be included in the Sequence Listing and the sequence identifier ("SEQ ID NO: X") must be used, either in the drawing or in the Brief Description of the Drawings."

Status of Application, Amendments and/or Claims

Claims 1-19 are pending in the instant application.

Election/Restrictions

In the 3/7/08 Office Action, Applicant's election without traverse of Group I, claims 1-10 and 12-19 was acknowledged, and claim 11 was withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim.

In addition, in the 3/7/08 Office Action, the previous elections of species were withdrawn and a new single election of species was set forth.

Applicant's response (received 3/26/08) to the election of species required in the 3/7/08 Office Action is acknowledged. Applicant elects species (2), SEQ ID NO: 9 (SKRSRLL) derived from human CD28 protein. Applicants state that the claims encompassing the elected species are claims 1-4, 6-10, 12 and 15-19. The Examiner agrees with this statement.

Claims 5, 13 and 14 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected species, there being no allowable generic or linking claim.

Claims 1-4, 6-10, 12 and 15-19 are under consideration, as they read upon the elected species.

Specification

The disclosure is objected to because of the following informalities:

(1) As noted above, Figure 1 contains two amino acid sequences, "SRRNRLLESD" and "SRRNRGESD" that are not present in the Sequence Listing as required by the rules for sequence compliance. Furthermore, the rules require that any sequence shown in a Figure be identified by the appropriate Sequence Identifier in either the Figure itself or in the Brief Description of the Figure.

Appropriate correction is required.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-4, 6-10, 12, 15 and 16 are rejected under 35 U.S.C. 102(b) as being anticipated by Truneh et al, 1996 (Molecular Immunology. 33(3): 321-334; reference C6 on the IDS filed 11/30/06).

Claim 1 encompasses a modified chimeric receptor comprising a chimeric receptor having a dileucine motif in its intracellular portion, wherein said modified chimeric receptor has a disruption in said dileucine. No limitation is placed on the nature of said disruption. Thus, the disruption broadly encompasses deletion of the entire dileucine motif followed by addition of different amino acids. Truneh et al teach a chimeric CD28-Ig fusion comprising the extracellular domain of human CD28 fused to an Ig molecule. This molecule is described in Figure 1 of Truneh et al, which shows that the CD28 portion ends with the residues GPSKP, which is residues 130-134 of the mature human CD28 protein. Because this chimeric receptor only includes the extracellular domain of CD28, it has a completion deletion of the dileucine motif of CD28 of SEQ ID NO: 9 (SKRSRLL), which is residues 163-169 of the mature human CD28 protein. Therefore, the teachings of Truneh et al anticipate claim 1.

Claim 2 depends from claim 1 and limits the dileucine motif to a group including the elected species of SEQ ID NO: 9. As described above, the chimeric receptor taught by Truneh et al only includes the extracellular domain of CD28 and therefore has a completion deletion of the dileucine motif of SEQ ID NO: 9. Therefore, the teachings of Truneh et al also anticipate claim 2.

Claim 3 depends from claim 1 and limits the dileucine motif to one derived from a CD28 protein. Therefore, the teachings of Truneh et al also anticipate claim 3.

Claim 4 depends from claim 3 and limits CD28 to human CD28 and the dileucine motif to SEQ ID NO: 9. Therefore, the teachings of Truneh et al anticipate claim 4 for the same reason as claim 2 above.

Claim 6 depends from claim 1 and limits the modified chimeric receptor to a T-cell receptor. As taught by Truneh et al, CD28 "serves as a co-signalling molecules for T-cell activation through its binding to its cognate counter-receptors CD80 and B70, expressed on antigen presenting cells" (Abstract). Therefore, the term "T-cell receptor" encompasses CD28, and claim 6 is anticipated by Truneh et al for the same reasons as claim 1 above.

Claim 7 depends from claim 1 and limits the disruption to comprising an addition of at least one residue within said dileucine motif. The claim does not require that any of the dileucine motif residues remain in the disrupted receptor. In the receptor taught by Truneh et al, amino acid residues from the Ig molecule have been added to the positions wherein the dileucine motif was originally present. Therefore, the teachings of Truneh et al also anticipate claim 8.

Claim 8 depends from claim 1 and limits the disruption to comprising a deletion of at least one amino within the dileucine motif. As described above, the chimeric receptor taught by Truneh et al includes deletion of all of the amino acids of the dileucine motif of SEQ ID NO: 9. Therefore, the teachings of Truneh et al also anticipate claim 8.

Claims 9 and 10 depend from claim 1 and each encompass a disruption wherein at least one leucine in the dileucine motif is substituted. In the chimeric receptor taught by Truneh et al, both leucines of the dileucine motif of SEQ ID NO: 9 have been replaced with residues from the Ig molecule. Therefore, the teachings of Truneh et al also anticipate claims 9 and 10.

Claims 12, 15 and 16 each encompasses a human CD28 protein or portion thereof having a disruption in a dileucine motif of SEQ ID NO: 9. Therefore, the teachings of Truneh et al described above also anticipate these claims.

Claims 1-4, 6-10, 12 and 15-19 are rejected under 35 U.S.C. 102(b) as being anticipated by Greenfield et al, 1997 (Journal of Immunology. 158: 2025-2034).

Greenfield et al teach a human CD28-Ig fusion (see pg 2026, right column). This molecule anticipates claims 1-4, 6-10, 12, 15 and 16 for the same reasons described above for the human CD28-Ig fusion taught by Truneh et al.

Greenfield et al further teach that BW1100 cells transfected with B7.2 cDNA ("BW1100-mB7.2") were able to bind to hCD28-Ig (pg 2030, right column). Greenfield et al teach that BW1100 cells are "a TCR αβ-deletion mutant of murine T cell tumor line BW5147" (pg 2029, right column); thus BW1100 cells are encompassed by the term "T-cell". Therefore, the BW1100-mB7.2 cells are T-cells having a modified chimeric receptor (CD28-Ig) "on its membrane" (because the CD28-Ig is bound the membrane of the BW1100 through binding to B7.2). Therefore, the teachings of Greenfield et al also anticipate instant claims 17-19.

Claims 1, 2, 6-10, 17 and 19 are rejected under 35 U.S.C. 102(b) as being anticipated by Haft et al, 1994 (Journal of Biological Chemistry. 269: 26286-26294; reference C3 on the IDS filed 11/30/06).

Claim 1 encompasses a modified chimeric receptor comprising a chimeric receptor having a dileucine motif in its intracellular portion, wherein said modified chimeric receptor has a disruption in said dileucine. No limitation is placed on the nature of said disruption. Haft et al teach, "The insulin receptor contains four dileucine pairs in its cytoplasmic domain. To determine if these insulin receptor sequences can serve as lysosomal sorting sequences, chimeric molecules expressing the Tac antigen fused to each isolated insulin receptor motif were constructed. A chimera containing the juxtamembrane dileucine motif (EKITLL), which closely resembles the sequence originally identified in the gamma- and epsilon- chains of the T cell receptor (DKQTLL and EVQLL), was shown to lysosomes ... exclusively cell surface staining was also seen for a chimera expressing a mutant motif (EKITAA), wherein the leucine residues were mutated to alanines" (see Abstract). This chimeric receptor expressing the mutant motif EKITAA taught by Haft et al anticipates claim 1.

Claim 2 depends from claim 1 and limits the dileucine motif to a group including SEQ ID NO: 3. The dileucine motif EKITLL is a sequence encompassed by SEQ ID NO:

3 (EXXXLL, wherein X is any amino acid). Therefore, the teachings of Haft et al described above also anticipate claim 2.

Claim 6 depends from claim 1 and limits the modified chimeric receptor to a T-cell receptor. The Tac antigen is also known as the interleukin-2 receptor α chain (pg 261288), which is expressed on T cells and is therefore encompassed by the term "T-cell receptor". Therefore, the chimeric receptor comprising the Tac antigen is also encompassed by the term "T-cell receptor". Therefore, the teachings of Haft et al also anticipate claim 6.

Claims 7 and 8 depend from claim and respectively limit the disruption to one comprising an addition (claim 7) or a deletion (claim 8) of at least one amino within the dileucine motif. These recitations do not require any particular sequence to be present following disruption, and therefore each recitation broadly encompasses deletion of residue (e.g. a leucine) combined with addition of a different amino acid (e.g. an alanine). As described above, the chimeric receptor taught by Haft et al combines deletion of two leucine residues of the dileucine motif with addition of two alanine residues. Therefore, the teachings of Haft et al also anticipate claims 7 and 8.

Claims 9 and 10 depend from claim 1 and each encompass a disruption wherein at least one leucine in the dileucine motif is substituted. In the chimeric receptor taught by Haft, both leucines of the dileucine motif have been replaced with alanine residues. Therefore, the teachings of Haft et al also anticipate claims 9 and 10.

Claim 17 encompasses a cell having on its membrane at least one modified chimeric receptor comprising a chimeric receptor having a dileucine motif in its intracellular portion, wherein said modified chimeric receptor has a disruption in said dileucine. As described above, Haft et al teach cell surface staining of the chimeric receptor comprising the EKITAA mutant motif. Therefore, the teachings of Haft et al described above also anticipate claim 17.

Claim 19 depends from claim 17 and limits the modified chimeric receptor to a T-cell receptor. As described above for claim 6, the chimeric receptor described by Haft et al is encompassed by the term "T-cell receptor". Therefore, the teachings of Haft et al anticipate claim 19 for the same reasons as claim 17.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-4, 6-9, 12, 15-19 are rejected under 35 U.S.C. 103(a) as being unpatentable over Parry et al, 1997 (Biochem J. 326: 249-257).

Parry et al teaches that the "CD28 cytoplasmic domain tails contains several potential phosphorylation sites around Ser^{163}, Ser^{166}, Thr^{177} and Thr^{184} for PKC" (pg 249, right column). As described above, the human CD28 cytoplasmic domain contains the dileucine motif of SEQ ID NO: 9 (SKRSRLL), which represents residues 163-169 of the mature human CD28 protein; therefore Ser^{163} and Ser^{166} are part of this dileucine motif. Parry further demonstrates that using Jurkat T-cells, "[p]hosphoamino acid analysis revealed that phosphorylation of CD28 after ligation by B7.1 occurred predominantly on serine/threonine residues (Figure 1B)" (pg 251, left column). Parry further teaches mutation of residues Tyr^{173} or Tyr^{200} to phenylalanine in the cytoplasmic domain of CD28 (pg 252-253). Parry further teaches expression of the mutated CD28 in DC27.1 murine T-cell hybridoma (pg 253, right column). Parry does not teach a chimeric receptor with a disruption in the dileucine motif.

It would have been obvious to the person of ordinary skill in the art at the time the invention was made to mutate (to phenylalanine as taught by Parry for tyrosine residues) each of residues Ser^{163}, Ser^{166}, Thr^{177} and Thr^{184} of CD28 both singly and in combination, and to further express the mutant CD28 in Jurkat T-cells for phosphoamino acid analysis of phosphorylation on serine/threonine residues after ligation by B7.1. The person of ordinary skill in the art would be motivated to do so in order to determine the residues required for serine/threonine phosphorylation of the cytoplasmic domain. Further, a person of ordinary skill in the art would have had a reasonable expectation of success because Parry teaches the techniques for mutation

of residues of the cytoplasmic domain of CD28, and in the absence of other evidence, the skilled artisan would expect such mutating techniques to work as well with the serine and threonine residues as with the tyrosine residues.

The specification does not provide a limiting definition of the term "chimeric receptor". Thus, the term encompasses mutated receptors with as little as one mutated amino acid; this single change renders the receptor chimeric because the altered amino acid is not found naturally in the receptor in that position. Thus, a CD28 with a mutated Ser^{163} and/or Ser^{166} residue(s) would be a chimeric receptor with a disruption of in the dileucine motif of SEQ ID NO: 9. This chimeric receptor would meet the limitations of each of claims 1-4, 6-9, 12, 15 and 16; and the Jurkat T-cells expressing this chimeric receptor would meet the limitations of claims 17-19. It is noted that claims 7 and 8 are included in this rejection because the recitation "addition" (claim 7) or "deletion" (claim 8) of at least one amino acid broadly encompasses both deletion of an amino acid followed by addition of an amino acid.

Conclusion

No claims are allowable.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Zachary C. Howard whose telephone number is 571-272-2877. The examiner can normally be reached on M-F 9:30 AM - 6:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary B. Nickol can be reached on 571-272-0835. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/Z. C. H./
Examiner, Art Unit 1646

/Elizabeth C. Kemmerer/
Primary Examiner, Art Unit 1646